222. (New) The oligonucleotide of claim 19 which comprises at least one ribonucleotide.

a4 cont

223. (New) The oligonucleotide of claim 221 comprising at least one 2'-O-methyl nucleotide.

224. (New) A kit comprising at least the oligonucleotide of claim 19.

Remarks

Claims 1-51 are pending in this application. Claims 1, 17, and 19 have been amended. Claims 207-224 have been added. These claims do not constitute new matter, as their support comes from claims 1, 17, 19, and 40-45 as originally filed. In addition, inadvertently made typographical errors in two references cited in the specification were corrected.

Each of the objections and rejections of the Office Action dated May 28, 1996 are addressed separately below.

I. Restriction Requirement

Claims 1-206 were subjected to a restriction requirement. Applicants elect the claims of Group I (1-51) without traverse for examination at this time. Claims 51-206 have been cancelled without prejudice for examination at a later date.

II. §102(b) Rejection

Claims 1, 17, 19, and 40-44 stand rejected under 35 U.S.C. §102(b) as being anticipated by either Wu et al. (1992) or Wu et al. (WO 93/04701-A1).

Claim 1 has been amended to exclude the oligonucleotides (having SEQ ID NOS:16 and 18) encompassed by the 21mer oligonucleotide disclosed in these Wu et al. references. Claims 17 and 19 have been amended to be in independent form and to recite that the oligonucleotide has a nucleotide sequence consisting of SEQ ID NO:16 (a 20mer) or NO:18 (a 12mer). New claims 207-224 are the same as claims 40-45, except that they are instead dependent directly or indirectly on amended claim 17 or 19.

Claims 1, 17, and 19 as amended are not anticipated by the Wu et al. references. Accordingly, this §102 rejection should be reconsidered and withdrawn. Likewise, the rejection of claims 40-44, which depend directly or indirectly from claim 1 and thus contain the limitations thereof, should also be reconsidered and withdrawn.

III. §103 Rejections

Claims 18 and 20 stand rejected under §103 as being obvious over either Wu et al. (1992) or Wu et al. (WO 93/04701-A1) in view of Ono et al. Applicants respectfully traverse this rejection.

Claim 18 is directed to an HBV RNA-specific oligonucleotide having SEQ ID NO:17 and being complementary to nucleotides 1903-1929 of the human HBV genome. Claim 20 is directed to an HBV RNA-specific oligonucleotide having SEQ ID NO:19 and being complementary to nucleotides 1910-1929 of the human HBV genome.

Wu et al. (1992) and Wu et al. (93/04701-A1) disclose a 21mer oligonucleotide complementary to nucleotides 1903-1923 of the human HBV genome. Ono et al. teaches the nucleotide sequence of HBV DNA.

The Examiner has noted that the oligonucleotide in the Wu et al. references encompasses applicants' claimed oligonucleotide having SEQ ID NO:16. Applicants note that applicants' oligonucleotide having SEQ ID NO:16 encompasses the subject oligonucleotide of claim 18 having SEQ ID NO:17, which is thus also encompassed by the Wu et al. oligonucleotide. However, neither the Wu et al. references nor the Ono reference alone or in combination teach or suggest oligonucleotides specifically

not true
SEQ ID NO 16 = 1903-1922
SEQ ID NO 17 = 1903-1929

complementary to nucleotides 1903-1929 or 1910-1929 of the human HBV genome. Neither do these references suggest that smaller oligonucleotides within the 1903-1923 targeted region of their oligonucleotide would also have activity.

The fact that the nucleotide sequence of an oligonucleotide overlaps, encompasses, or is included within the nucleotide sequence of another oligonucleotide proven to have antisense activity has no predictive value, as one with skill in the art is aware that adding and/or deleting a few nucleotides to an oligonucleotide can abolish its antisense activity (see, e.g., Westermann et al. (*Biomed. Biochim. Acta* (1989) **48**:85-93) in which adding 4 or 7 bases to either end of an effective oligonucleotide sequence eliminated its antisense activity (copy enclosed as Exhibit A); Daibata et al. (1996) *Antiviral Research* **29**:243-260), in which adding and/or deleting as few as two to eight bases from the ends of an oligonucleotide eliminated its antisense activity (copy enclosed as Exhibit B); and compare Ecker et al. (1993) *Nucleic Acids Research* **21**:1853-1856) and Lima et al. (1992) *Biochemistry* **31**:12055-12061) (copies enclosed as Exhibit C), in which a 10mer oligonucleotide binds to complementary H-ras RNA with 10X the efficiency that a 9mer oligonucleotide contained within the 10mer binds, suggesting that a difference of as few as one nucleotide at the end of an oligonucleotide may effect its antisense activity; and Matsukura et al. (1989) *Proc. Natl. Acad. Sci. (USA)* **86**:4244-4248 (copy

enclosed as Exhibit D), in which some antisense oligonucleotides directed to portions of the *gag* region of HIV-1 have no inhibitory activity). The references within Exhibits A-D teach away from the Examiner's contention that smaller oligonucleotides whose sequences fall within or overlap larger known sequences would, *de facto*, have the same activity and are obvious in view of such known sequences.

Thus this §103 rejection of claims 18 and 20 should be reconsidered and withdrawn.

Claims 46 and 47 stand rejected under §103 are being obvious in view of Wu et al. (WO 93/04701-A1) and Uhlmann et al.

Wu et al. teach a polydeoxynucleotide corresponding to nucleotides 1903-1923 of the human HBV genome and consisting essentially of deoxynucleotides linked with phosphorothioate internucleotide linkages or a polyribonucleotide corresponding to nucleotides 1903-1923 of the human HBV genome. Uhlmann et al. discloses oligonucleotides containing 2'-O-methyl ribonucleotides and oligonucleotides containing both ribonucleotides and deoxyribonucleotides.

Claim 46 recites an oligonucleotide of claim 1 comprising at least one ribonucleotide and at least one deoxyribonucleotide. Claim 47 recites an oligonucleotide of claim 1 comprising at

least one 2'-O-methyl ribonucleotide. Claim 1 as amended (upon which claims 46 and 48 depend) no longer includes oligonucleotides having a nucleotide sequence corresponding to nucleotides 1903-1922 of the human HBV genome.

This amendment to claim 1 is believed to obviate the rejection of claims 46 and 47 under §103. Accordingly, withdrawal of this rejection is respectfully requested.

Regarding independent claims 17 and 19 as amended and new claims 213 and 221 dependent on claims 17 and 19, respectively, a similar anticipated 103 rejection based on the Wu et al. (WO 93/04701-A1) and Uhlmann et al. references is respectfully traversed.

Claims 17 and 19 (as amended) recite oligonucleotides complementary to a portion of the HBV RNA and having a nucleotide sequence consisting essentially of the nucleotide sequence set forth as SEQ ID NO:16 (1903-1922) and NO:18 (1910-1921), respectively. New claims 213 and 221 are directed to the oligonucleotides of claims 17 and 19 having at least one deoxyribonucleotide and at least one ribonucleotide which may be a 2'-O-methyl ribonucleotide.

Wu et al. teach a polydeoxynucleotide corresponding to nucleotides 1903-1923 of the human HBV genome and consisting

essentially of deoxynucleotides linked with phosphorothioate internucleotide linkages or a polyribonucleotide corresponding to nucleotides 1903-1923 of the human HBV genome. This reference neither teaches nor suggests shorter oligonucleotides corresponding to the 20mer and 12mer oligonucleotide sequences set forth in applicants' SEQ ID NOS:16 and 18, respectively. Neither does this reference teach or suggest oligonucleotides of any sequence containing both deoxyribonucleotides and ribonucleotides. Nor does this reference teach or suggest an oligonucleotide of any nucleotide sequence having at least one 2'-O-methyl ribonucleotide.

Uhlmann et al. discloses oligonucleotides containing 2'-O-methyl ribonucleotides and oligonucleotides containing both ribonucleotides and deoxyribonucleotides. This reference neither teaches nor suggests HBV-specific oligonucleotides or oligonucleotides corresponding to the oligonucleotide sequences set forth as SEQ ID NOS:16 or 18 in applicants' claims 17 and 19.

Neither Wu et al. nor Uhlmann et al. alone or in combination teach or suggest oligonucleotides specifically complementary to nucleotides 1903-1929 or 1910-1929 of the human HBV genome. Neither do these references suggest that smaller oligonucleotides within the 1903-1923 targeted region of their oligonucleotide would also have activity. As discussed above, the fact that the nucleotide sequence of an oligonucleotide overlaps, encompasses,

or is included within the nucleotide sequence of another oligonucleotide proven to have antisense activity has no predictive value, as one with skill in the art is aware that adding and/or deleting a few nucleotides to an oligonucleotide can abolish its antisense activity (see, e.g., Exhibits A, B, C and D described above which teach away from the Examiner's obviousness rejection).

Thus this anticipated §103 rejection should be reconsidered and withdrawn.

Claims 1-9, 33-35, and 37-39 were rejected under 35 U.S.C. §103 as being obvious in view of Oh et al. and Ono et al. Applicants respectfully traverse this rejection.

Claims 1-9, 33-35, and 37-39 as amended are drawn to HBV-specific oligonucleotides having SEQ ID NOS:1-15, 17, 19-31, and 42-48.

Oh et al. discloses the inhibition of the expression of HBV surface antigen (HBsAg) using oligonucleotides directed to the HBV X and S genes, and discloses the inhibition of HBV proliferation using oligonucleotides directed to the HBV X and P genes. Ono et al. teaches the nucleotide sequence of human HBV DNA.

Neither of these references alone or in combination teaches or suggests applicants particular HBV-specific oligonucleotides having the nucleotide sequences set forth in the claims as SEQ ID NOS:1-15, 17, 19-31, and 42-48. Furthermore, oligonucleotides directed to other nucleotide sequences of the HBV genome are not predictive of the specific nucleotides set forth in applicants claims, as one with ordinary skill in the art is aware that even minor changes in the position and length of an oligonucleotide may greatly influence its antisense activity (see Exhibits A, B, C and D described above which teach away from the Examiner's obviousness rejection).

Thus, this §103 rejection should be reconsidered and withdrawn.

Claims 1-4, 15-35, 37-39, 44, 50 and 51 were rejected under 35 U.S.C. §103 as being obvious in view of Offenberger et al. and Ono et al. Applicants respectfully traverse this rejection.

Claims 1-4, 15-35, 50 and 51 as amended are directed to oligonucleotides and pharmaceutical compositions containing oligonucleotides having SEQ ID NOS:1-15, 17, 19-31, and 42-48.

Offenberger teaches oligonucleotides complementary to the duck HBV genome. This reference neither teaches nor suggests

oligonucleotides specific for human HBV RNA. Ono et al. teaches the nucleotide sequence of human HBV DNA.

Neither of these references alone or in combination teaches or suggests applicants particular human HBV-specific oligonucleotides having the nucleotide sequences set forth in the claims as SEQ ID NOS:1-15, 17, 19-31, and 42-48. Furthermore, as described above, oligonucleotides directed to other nucleotide sequences of the HBV genome from another species (i.e., duck) are not necessarily predictive of the specific nucleotides set forth in applicants claims, as one with ordinary skill in the art is aware that even minor changes in the position and length of an oligonucleotide may greatly influence its antisense activity (see Exhibits A, B, C and D described above which teach away from the Examiner's obviousness rejection).

Thus, this §103 rejection should be reconsidered and withdrawn.

Claims 1-9, 14-18, 33-35, and 37-44 stand rejected under 35 U.S.C. §103 as being obvious in view of Zhenghong et al. and Ono et al. Applicants respectfully traverse this rejection.

Claims 1-9, 14-18, 33-35, and 37-44 as amended are drawn to HBV-specific oligonucleotides having SEQ ID NOS:1-15, 17, 19-31, and 42-48, to such oligonucleotides having at least one

deoxyribonucleotide, and to such oligonucleotides which are modified such as by having various internucleotide linkages such as phosphorothioate linkages.

Zhenghong et al. disclose four oligonucleotides directed against nucleotides 1893-1907, 2297-2313, 2797-2813, and 1817-1831 of the HBV genome used to inhibit the expression of the HBsAg. Ono et al. teaches the nucleotide sequence of human HBV DNA.

Neither of these references alone or in combination teaches or suggests applicants particular HBV-specific oligonucleotides having the nucleotide sequences set forth in the claims as SEQ ID NOS:1-15, 17, 19-31, and 42-48. Furthermore, as described above, oligonucleotides directed to other nucleotide sequences of the HBV genome are not predictive of the specific nucleotides set forth in applicants claims, as one with ordinary skill in the art is aware that even minor changes in the position and length of an oligonucleotide may greatly influence its antisense activity (see Exhibits A, B, C and D described above which teach away from the Examiner's obviousness rejection).

Thus, this §103 rejection should be reconsidered and withdrawn.

Claims 1-40, 44, 45, 48, and 49 stand rejected under 35 U.S.C. §103 as being obvious in view of Bresser et al. and Ono et al. Applicants respectfully traverse this rejection.

Claims 1-40, 44, 45, 48, and 49 as amended are drawn to HBV-specific oligonucleotides having SEQ ID NOS:1-15, 17, 19-31, and 42-48, to such oligonucleotides having at least one deoxyribonucleotide, at least one ribonucleotide, and to kits containing at least one or two of such oligonucleotides.

Bresser et al. teaches in situ hybridization using oligonucleotide probes complementary to the HIV, EBV, and CMV genome. This reference neither teaches nor suggests oligonucleotides specific for human HBV RNA. Ono et al. teaches the nucleotide sequence of human HBV DNA.

The combination of these references do not result in applicants' claimed invention, as neither of these references teaches or suggests antisense oligonucleotides complementary to the HBV genome or applicants' particular HBV-specific oligonucleotides having the nucleotide sequences set forth in the claims as SEQ ID NOS:1-15, 17, 19-31, and 42-48. Neither do these references alone or in combination teach or suggest modified HBV-specific oligonucleotides or HBV-specific oligonucleotides with at least one deoxyribonucleotide or ribonucleotide. In addition, these references alone or in

combination do not teach or suggest kits containing at least one or two of such HBV-specific oligonuleotides.

Thus, this §103 rejection should be reconsidered and withdrawn.

IV. Conclusions

On the basis of the above amendments and remarks, this application is believed to be in condition for allowance. Accordingly, reconsideration of this application and its allowance are requested.

A Request for a One Month Extension of Time along with the required fee of $110.00. Please charge any additional fees or credit any overpayments to our Deposit Account No. 08-0219.

The Examiner is encouraged to call the undersigned to facilitate prosecution.

Respectfully submitted,

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Date: September 25, 1996